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Date of mailing (day/month/year) 04 February 1999 (04.02.99)	in its capacity as elected Office				
International application No. PCT/IE98/00036	Applicant's or agent's file reference FB3782/MOC				
International filing date (day/month/year) 14 May 1998 (14.05.98)	Priority date (day/month/year) 14 May 1997 (14.05.97)				
Applicant					
PASSMORE, Clare et al					
The designated Office is hereby notified of its election mad     in the demand filed with the International Preliminary					
14 December	1998 (14.12.98)				
in a notice effecting later election filed with the International Bureau on:					
2. The election X was was not					
made before the expiration of 19 months from the priority of Rule 32.2(b).	date or, where Rule 32 applies, within the time limit under				

The International Bureau of WIPO 34, chemin des Colombettes	Authorized officer  Yolaine CUSSAC	
1211 Geneva 20, Switzerland		

# INTERNATIONAL SEARCH REPORT



Inte ..ional Application No PCT/IE 98/00036

A. CLASSIFICATION OF SUBJECT MATTER
1PC 6 A61K9/107 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

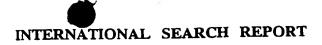
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.			
Х	WO 91 04733 A (THE MENTHOLATUM COMPANY LIMITED) 18 April 1991	1,2,9, 14-18			
Α	see page 5; example 1	3-8, 10-13			
X	WO 97 04728 A (ZHANG ET AL.) 13 February 1997 see page 18, line 14 - line 31	1,2,9, 14-18			
X	A.A. NYQUIST-MAYER ET AL.: "Drug release studies on an oil-water emulsion based on a eutectic mixture of lidocaine and prilocaine as the dispersed phase" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 75, no. 4, April 1986, pages 365-373, XP002078799 Washington (US) see page 365	1,2,9, 14-18			
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X Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
Special categories of cited documents:  "A" document defining the general state of the art which is not considered to be of particular relevance  "E" earlier document but published on or after the international filing date  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  "O" document referring to an oral disclosure, use, exhibition or other means  "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  "&" document member of the same patent family
Date of the actual completion of theinternational search	Date of mailing of the international search report
28 September 1998	08/10/1998
Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2	Authorized officer
NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K





Int. tional Application No PCT/IE 98/00036

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	ation) DOCUMENTS CONSIDERED TO BE RELEVANT			
Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to daim No.		
X	EP 0 485 207 A (RHONE-POULENC AGROCHIMIE) 13 May 1992 see page 7, line 8 - line 12 see page 20 - page 21; example 3	1,2,9,14		



Information on patent family members

Inte ional Application No PCT/IE 98/00036

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		TR 25517 A	01-05-1993

#### **CLAIMS**

- 1. A topical composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of first and second pharmacologically active agents and the continuous phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C.
- 2. A topical composition according to Claim 1, in which the first pharmacologically active agent has a melting point between 35 and 75°C, preferably 40-50°C, and the second pharmacologically active agent has a melting point between -40 and 150°C, preferably between -5 and 90°C.
- 15 3. A topical composition according to Claim 1 or 2, in which the topical composition additionally includes, in the eutectic mixture, a third pharmaceutically acceptable component.
- 4. A topical composition according to Claim 3, in which the third pharmaceutically acceptable component has a melting point between 40 and 150°C, preferably between 40 and 75°C.
  - 5. A topical composition according to Claim 3 or 4, in which the third component is a third pharmacologically active agent.
- 25 6. A topical composition according to any one of Claims 3-5, in which the topical composition additionally includes, in the eutectic mixture, a fourth pharmaceutically acceptable component.

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- 7. A topical composition according to Claim 6, in which the fourth pharmaceutically acceptable component has a melting point between 40 and 150°C, preferably between 40 and 75°C.
- 8. A topical composition according to Claim 6 or 7, in which the fourth component comprises a fourth pharmacologically active agent.
- 9. A topical composition according to any one of the preceding claims, in which said compositions contain no cosolvent or additional oil phase, so that the eutectic mixture substantially, preferably essentially, comprises the or each discontinuous phase of the emulsion.
- 10. A topical composition according to any one of the preceding claims, in which the first pharmacologically active agent is selected from triclosan, chlorocresol, chlorbutanol, methyl nicotinate, triprolidine, promethazine, trimeprazine, sulfiram, oxybutynin, capsaicin, testosterone enanthate or choline salicylate.
- A topical composition according to any one of the preceding claims, in which the second pharmacologically active agent is selected from triclosan; chlorocresol, 20 capsaicin, trimeprazine, choline salicylate, methyl nicotinate; non-steroid anti-inflammatory agents selected from arylpropionic acid derivatives such as ibuprofen, ketoprofen, fenoprofen and flurbiprofen; aryl acetic acid derivatives such as etodolac; and arylcarboxylic acids; 25 narcotic analgesics such as fentanyl; anti-fungal agents such as econazole and ketoconazole; antibacterial agents such as mupirocin, chlorbutanol, clindamycin and iodine; anticholinergics such as oxybutynin; anthelmintics such as tetramisole; antihistaminics such as triprolidine and 30 promethazine and antihypertensives such as propranolol.

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12. A topical composit on according to Claim 5 or 8, in which the third and fourth pharmacologically active agents are each selected from triclosan; chlorocresol; capsaicin, trimeprazine, choline salicylate, methyl nicotinate; non-steroid anti-inflammatory agents selected from arylpropionic acid derivatives such as ibuprofen, ketoprofen, fenoprofen and flurbiprofen; aryl acetic acid derivatives such as etodolac; and arylcarboxylic acids; narcotic analgesics such as fentanyl; anti-fungal agents such as econazole and ketoconazole; antibacterial agents such as mupirocin, chlorbutanol, clindamycin and iodine; anticholinergics such as oxybutynin; antihypertensives such as propranolol; antihistaminics such as triprolidine and promethazine; and anthelmintics such as tetramisole.

- 13. A topical composition according to Claim 3 or 4, in which the third pharmaceutically acceptable component is lauric acid, stearyl alcohol, menthol, thymol, cinnamic acid or an ester thereof.
- 14. A topical composition according to any one of the
  20 preceding claims, in which the pharmaceutically acceptable
  carrier is substantially hydrophilic, said carrier containing
  substantially, preferably essentially, water as the
  continuous phase.
- 15. A topical composition according to any one of the
  25 preceding claims, in which the pharmaceutically acceptable
  carrier contains at least one gelling or suspension agent.
  - 16. A topical composition according to Claim 15, in which the gelling or suspension agent is selected from carbomers, modified cellulose derivatives, naturally-occurring,
- 30 synthetic or semi-synthetic gums such as xanthan gum, acacia and tragacanth, modified starches, co-polymers such as those

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formed between maleic anhydride and methyl vinyl ether, colloidal silica and methacrylate derivatives or a mixture thereof.

- 17. A topical composition according to any one of the preceding claims, in which the pharmaceutically acceptable carrier includes at least one surfactant compatible with any pharmacologically active agents or pharmaceutically acceptable components present.
- 18. A topical composition according to any one of the 10 preceding claims, in which the topical composition is in the form of a gel, lotion, suspension, cream, aerosol spray, transdermal patch, medicated dressing or soft gelatin capsule.



### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	rence FOR FURTHER see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.			
FB3782/MOC	ACTION			
International application No.	International filing date (day/month/year) (Earliest) Priority Date (day/month/year)			
PCT/IE 98/00036	14/05/1998 14/05/1997			
Applicant				
CALEN (CHEMICALS) LIMITED	o+ a1			
GALEN (CHEMICALS) LIMITED	et al.			
This International Search Report has been according to Article 18. A copy is being tra	n prepared by this International Searching Auth Insmitted to the International Bureau.	nority and is transmitted to the applicant		
This International Search Report consists  It is also accompanied by a copy	of a total of4 sheets.  y of each prior art document cited in this report.			
Certain claims were found un	searchable(see Box I).			
2. Unity of Invention is lacking (s	ee Box II).			
	ntains disclosure of a nucleotide and/or amino out on the basis of the sequence listing	o acid sequence listing and the		
	with the international application.			
furn	ished by the applicant separately from the inter	rnational application,		
	but not accompanied by a statement to the matter going beyond the disclosure in the	e effect that it did not include international application as filed.		
Trai	nscribed by this Authority			
4. With regard to the title, X the	text is approved as submitted by the applicant			
the	text has been established by this Authority to re	ead as follows:		
5. With regard to the abstract,				
	text is approved as submitted by the applicant text has been established, according to Rule 3			
Box	III. The applicant may, within one month from Irch Report, submit comments to this Authority	the date of mailing of this International		
6. The figure of the drawings to be publ	ished with the abstract is:			
Figure No as s	suggested by the applicant.	None of the figures.		
bec	ause the applicant failed to suggest a figure.			
bec	ause this figure better characterizes the invent	ion.		



#### INTERNATIONAL SEARCH REPORT

iternational application No.

PCT/IE 98/00036

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The invention concerns a topical composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of first and second pharmacologically active agents and the continuous phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°. The topical composition may additionally comprise, in the eutectic mixture, a third or fourth pharmaceutically acceptable component.

According to Intermational Patent Claselfication (PC) or to both national claselfication and IPC  8. FIELDS SEARCHED  Winners documentation searched (claselfication system followed by claselfication symbots)  IPC 6 A61K  Documentation searched other than minimum-documentation to the custorit that such documents are included in the fields searched  Electronic data base consulted during the international search (name of data base and, where practical, search forms used)  C.DOCUMENTS CONSIDERED TO BE RELEVANT  Calegopy * Citation of document, with indication, where appropriate, of the relevant passages  X W0 91 04733 A (THE MENTHOLATUM COMPANY LIMITED) 18 April 1991  A see page 5; example 1  X W0 97 04728 A (ZHANG ET AL.)  13 February 1997  see page 18, 11ne 14 — 11ne 31  X A.A. NYOUIST—MAYER ET AL.: "Drug release studies on an oil—water emulsion based on a cutectric mixture of 1 idocatine and pril ocatine as the dispersed phase" JOURNAL OF PHARMACEUTICAL SCIENCES, vol 7.5, no. 4, April 1986, pages 365–373, XPO02078799  Washington (US) see page 365  X Putther documents are listed in the continuation of box C.  X Futther documents are listed in the continuation of box C.  X Futther documents are listed in the continuation of box C.  X Futther documents are listed in the continuation of box C.  X Futther documents are listed on the art which is not considered to be of particular indications and incomplete the page of the page o	A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K9/107 A61K45/06						
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# **PCT**

REC'D 16 SEP 1999

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's	or age	nt's file reference		See Notification	of Transmittal of International	
FB3782/N	<b>NOC</b>		FOR FURTHER ACTION	ACTION Preliminary Examination Report (Form PCT/IPEA/416)		
Internationa	l appli	cation No.	International filing date (day/mont	n/year) Prid	ority date (day/month/year)	
PCT/IE98	3/000	36	14/05/1998	14	/05/1997	
Internationa A61K9/10		nt Classification (IPC) or na	tional classification and IPC			
Applicant						
GALEN (	CHE	MICALS) LIMITED et	al.			
and is	trans	smitted to the applicant a	according to Article 36.		onal Preliminary Examining Authority	
2. This F	REPO	RT consists of a total of	7 sheets, including this cover s	heet.		
b (s	een a see R	mended and are the bas	sis for this report and/or sheets 07 of the Administrative Instruct	containing rectific	aims and/or drawings which have ations made before this Authority CT).	
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3. This r	eport	contains indications rela	ating to the following items:			
1	$\boxtimes$	Basis of the report				
ti.		Priority				
111			ppinion with regard to novelty, in	ventive step and	industrial applicability	
IV		Lack of unity of invention				
V	⊠		nder Article 35(2) with regard to ons suporting such statement	novelty, inventive	e step or industrial applicability;	
VI		Certain documents cit	ed			
VII	$\boxtimes$	Certain defects in the i	nternational application			
VIII		Certain observations o	n the international application			
Date of sub	missic	on of the demand	Date of	completion of this r	eport	
14/12/19	98			14.0	g, 90 	
		address of the internationa	al Author	zed officer	SASONS MILLI	
preliminary		ining authority:				
		ppean Patent Office 0298 Munich	Simo	, F		
		+49 89 2399 - 0 Tx: 52365 +49 89 2399 - 4465	6 epmu d	one No. +49 89 239	0 3083	

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IE98/00036

1.	Bas	is of the report				
	This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):					
	Des	cription, pages:				
	1-20	)	as originally filed			
	Clai	ms, No.:				
	1-24	ļ	as received on	20/08/1999	with letter of	19/08/1999
	Dra	wings, sheets:				
	1-9		as originally filed			
2.	The	amendments have	e resulted in the cancellation of:			
		the description,	pages:			
		the claims,	Nos.:			
		the drawings,	sheets:			
3.	×		en established as if (some of) t beyond the disclosure as filed (		nts had not been made	e, since they have been
		see separate she	eet			
4.	Add	itional observations	s, if necessary:			
111.	Nor	n-establishment of	f opinion with regard to nove	lty, inventive	step and industrial a	pplicability
			e claimed invention appears to able have not been examined i		volve an inventive ste	p (to be non-obvious),
		the entire internati	ional application.			
	×	claims Nos. 21,23				

because:

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IE98/00036

	Ø	the said international application, or the said claims Nos. 21,23 relate to the following subject matter whi does not require an international preliminary examination (specify):					
		see separate sheet					
		the description, claims o that no meaningful opini			eate particular elements below) or said claims Nos. are so unclear ed (specify):		
		the claims, or said claim could be formed.	s Nos.	are so in	adequately supported by the description that no meaningful opinion		
		no international search	report h	as been e	established for the said claims Nos		
٧.					ith regard to novelty, inventive step or industrial upporting such statement		
1.	Stat	tement					
	Nov	velty (N)	Yes: No:	Claims Claims	1-20,22		
	Inve	entive step (IS)	Yes: No:	Claims Claims	1-20,22		
	Indi	ustrial applicability (IA)	Yes: No:	Claims Claims	1-20,22		
2.	Cita	ations and explanations					
	see	e separate sheet					
VI	l. Ce	ertain defects in the inte	rnation	al applic	ation		
Th	ne fol	llowing defects in the forr	n or cor	ntents of t	he international application have been noted:		

see separate sheet

ı

The amendments filed with the letter dated 19.08.1999 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following: present claim 24 deals with eutectic mixtures of specific compounds. Even though said specific compounds are mentioned in examples A-I and examples 3 and 6 in the description as filed, said compounds are only disclosed in relation to a specific ratio for which the eutectic mixture is liquid at 20°C (see eg example B and fig. 2), in a specific composition (see example 3, "emulsified gel preparation suitable for treating allergic and inflammatory pruritic skin compositions") and only for exactly two compounds and not for at least two compounds. Present claim 24 does not refer to each of these features and its subject-matter is therefore broader than that disclosed in the application as filed.

Ш

The subject-matter of claims 21 and 23 is directed to a method for treatment of the human body by therapy (Art. 34(4)(a)(i) and Rule 67.1(iv) PCT).

V

- 1 Reference is made to the following documents:
  - D3: WO 91 04733 A (THE MENTHOLATUM COMPANY LIMITED) 18 April 1991
  - D4: WO 97 04728 A (ZHANG ET AL.) 13 February 1997
  - D5: A.A. NYQUIST-MAYER ET AL.: "Drug release studies on an oil-water emulsion based on a eutectic mixture of lidocaine and prilocaine as the dispersed phase" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 75, no. 4, April 1986, pages 365-373, XP002078799 Washington (US)
  - D6: EP 0 485 207 A (RHONE-POULENC AGROCHIMIE) 13 May 1992
- 2 Novelty (Art. 33(2) PCT)

The subject-matter of present claims 1-20 and 22 fulfills the requirements of Art. 33(2) PCT.

2.1 Document D3 (see D3, page 3, lines 3-10 and eg. example 3 on page 6)

discloses eg a composition containing a eutectic solution of 4 g ibuprofen and 4 g menthol, also mixed with benzyl alcohol, carbomer and water. However, none of the compositions of D3 contains an emulsifying agent. Therefore, the subject-matter of present independent claim 1 and present independent claim 22 is new over D3.

- 2.2 Document D4 discloses a formulation, which is a gelled oil-in-water emulsion with an oil phase being a eutectic mixture of local anaesthetics. In a particular embodiment (see D4, example 1, page 18), the composition comprises an aqueous continuous phase with a polymeric emulsifier and an oil phase consisting of a eutectic mixture of lipocaine and tetracaine stated as being liquid at room temperature. However, present independent claim 1 and present independent claim 22 disclaim compositions comprising local anaesthetics. Thus, present independent claims 1 and 22 are new over D4.
- 2.3 Document D5 discloses a topical anaesthetic formulation based on a 1:1 eutectic mixture, having an eutectic temperature of 18°C, of lidocaine and prilocaine, emulsified in water. Present independent claim 1 and present independent claim 22 disclaim compositions comprising local anaesthetics. For this reason, present independent claims 1 and 22 are new over D5.
- 2.4 Document D6 discloses a stabilized pesticidal emulsion of the oil-in-water type (see D6, page 4, lines 39-45) comprising (see D6, pages 20-21, example 3):
  - an oil phase consisting of two pesticides: 191 g/l (2,4-dichlorophenoxy)acetic acid isooctyl ester (2,4-D IOE)and 208 g/l (2,4-dichlorophenoxy)propionic acid isooctyl ester (2,4-DP IOE),
  - a water phase containing surfactants and thickeners.

Even though said pesticides are ingredients which are pharmacologically active and are liquid at room temperature (see D6, page 19, lines 33- 37 and page 7, lines 8-12), present independent claim 1 and present independent claim 22 refer to topical compositions for mutual enhancement of transdermal permeation of pharmacologically active ingredients. It is clear that compositions containing pesticides, ie substances which are virtually toxic to humans, are not topical compositions suitable for transdermal permeation in the meaning of the present application.

### 3 Inventive step (Art. 33(3) PCT)

Document D4 is devoted to an apparatus, a product formulation and a method for improved dermal permeation of pharmaceuticals. The subject-matter of D4 belongs also to the medical field and document D4 can be therefore considered as the closest prior art for present application.

As stated above (point 2.2), the subject-matter of present claim 1 differs from the known composition in that it does not contain local anaesthetics.

The problem to be solved by the present invention may therefore be regarded as how to enhance mutually the topical absorption of at least two drugs, regardless their nature (see present application p. 1, I. 3-12 and p. 4, I. 8-18).

Document D4 teaches the skilled person that a composition comprising a eutectic mixture of local anaesthetics is chemically more stable: the active ingredients are less subject to hydrolytic degradation. Even though document D4 points out that the device can be used for delivering a multitude of drugs, the teaching of D4, regarding a eutectic mixture, is confined to anaesthetics and more particularly to the their stability (see D4, p. 10, l. 6 - p. 13, l. 7). There is no incentive in D4 to consider the applicability of a eutectic mixture for anything other than hydrolysis-sensitive local anaesthetics, and even less for increasing the mutual enhancement of the topical absorption of at least two drugs. In D4, the improvement of the dermal permeation is due to heat supplied by the device, regardless of the formulation, eutectic or non-eutectic. The present application does not require the use of heat to achieve a similar aim.

For these reasons, the subject-matter of independent claim 1 seems to include an inventive step in the meaning of Art. 33(3) PCT.

This reasoning applies mutatis mutandis to the subject-matter of present independent claim 22.

- 4 Claims 2-20 are dependent on independent claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.
- For the assessment of the present claims 21 and 23 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the

International application No. PCT/IE98/00036

**EXAMINATION REPORT - SEPARATE SHEET** 

use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment (present claim 22).

#### VII

- Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art 1 disclosed in the documents D3-D5 is not mentioned in the description, nor are these documents identified therein.
- 2 The description is not in conformity with the claims as required by Rule 5.1(a)(iii) PCT.



# From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

O'CONNELL, Maura F.R. KELLY & CO 9 University Street Belfast BT7 1NA Northern Ireland GRANDE BRETAGNE

## PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)

Date of mailing (day/month/year)

14, 03, 99

Applicant's or agent's file reference

International application No.

FB3782/MOC

PCT/IE98/00036

International filing date (day/month/year)

14/05/1998

Priority date (day/month/year)

IMPORTANT NOTIFICATION

14/05/1997

Applicant

GALEN (CHEMICALS) LIMITED et al.

- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office D-80298 Munich

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Fax: +49 89 2399 - 4465

Authorized officer

Bleeker, M

Tel.+49 89 2399-8141





# **PCT**

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

1		_	ent's file reference	FOR FURTHER ACTIO	ON .		ation of Transmittal of International  Examination Report (Form PCT/IPEA/416)		
FB	3782/1	MOC	·						
			ication No.	International filing date (day/month/year)		'year)	Priority date (day/month/year)		
PC	T/IE98	3/000	)36	14/05/1998			14/05/1997		
	rnationa 1K9/10		ent Classification (IPC) or na	tional classification and IPC					
1	oticant LEN (	CHE	MICALS) LIMITED et	al.					
1.			ational preliminary exam smitted to the applicant a		pared	by this Inte	ernational Preliminary Examining Authority		
2.	This F	REPO	ORT consists of a total of	7 sheets, including this cov	ver sh	eet.			
	b	een a	mended and are the ba	d by ANNEXES, i.e. sheets sis for this report and/or she 07 of the Administrative Inst	ets c	ontaining re	n, claims and/or drawings which have ectifications made before this Authority ne PCT).		
	These	ann	exes consist of a total of	7 sheets.					
3.	This r	eport	contains indications rela	ating to the following items:					
	1	$\boxtimes$	Basis of the report						
	Ш		· ·						
	Ш	$\boxtimes$	Non-establishment of o	pinion with regard to novelt	novelty, inventive step and industrial applicability				
	IV		Lack of unity of invention	1					
•	٧	×		nder Article 35(2) with regar ons suporting such stateme		novelty, inve	entive step or industrial applicability;		
	VI		Certain documents cit	ed					
	VII	$\boxtimes$	Certain defects in the in	nternational application					
	VIII		Certain observations o	n the international applicatio	n				
Date	e of sub	missio	on of the demand	Da	te of c	ompletion of	·		
14/	12/199	98					} <b>4. 03. 99</b>		
			g address of the international	ai Au	thorize	ed officer	AND CO M. D. Co.		
	<u>o</u> ))	D-80	ppean Patent Office 0298 Munich +49 89 2399 - 0 Tx: 52365		mon,	F	Transport		
-			: +49 89 2399 - 4465	Telephone No. +49 89 2399 2083					

## INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No. PCT/IE98/00036

in

١.	Ba	sis	of	the	re	po	rt
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1.	This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):									
	Des	scription, pages:								
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	Cla	ims, No.:								
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	Dra	wings, sheets:								
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		the drawings.	sheets:							
3.	Ø		een established as if (some of) tl beyond the disclosure as filed (F		its had not been made	e, since they have been				
		see separate she	eet							
4.	Add	litional observations	s, if necessary:							
					•					
111.	Nor	n-establishment of	f opinion with regard to novel	ty, inventive	step and industrial a	pplicability				
			e claimed invention appears to table have not been examined in		volve an inventive stel	p (to be non-obvious),				
		the entire internati	ional application.							
	×	claims Nos. 21.23								

because:

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IE98/00036

	the said international application, or the said claims Nos. 21,23 relate to the following subject matter whice does not require an international preliminary examination ( <i>specify</i> ):				
		see separate sheet			
		the description, claims of that no meaningful opin			cate particular elements below) or said claims Nos. are so unclear led (specify):
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٧.					ith regard to novelty, inventive step or industrial upporting such statement
1.	Stat	tement			
	Nov	velty (N)	Yes: No:	Claims Claims	1-20,22
	Inve	entive step (IS)	Yes: No:	Claims Claims	1-20,22
	Indi	ustrial applicability (IA)	Yes: No:	Claims Claims	1-20,22
2.	Cita	ations and explanations			
	see	separate sheet			
VI	I. Ce	rtain defects in the inte	rnation	al applic	ation
Th	e fol	lowing defects in the form	n or cor	ntents of t	he international application have been noted:

see separate sheet

## **EXAMINATION REPORT - SEPARATE SHEET**

The amendments filed with the letter dated 19.08.1999 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following: present claim 24 deals with eutectic mixtures of specific compounds. Even though said specific compounds are mentioned in examples A-I and examples 3 and 6 in the description as filed, said compounds are only disclosed in relation to a specific ratio for which the eutectic mixture is liquid at 20°C (see eg example B and fig. 2), in a specific composition (see example 3, "emulsified gel preparation suitable for treating allergic and inflammatory pruritic skin compositions") and only for exactly two compounds and not for at least two compounds. Present claim 24 does not refer to each of these features and its subject-matter is therefore broader than that disclosed in the application as filed.

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D6: EP 0 485 207 A (RHONE-POULENC AGROCHIMIE) 13 May 1992

#### 2 Novelty (Art. 33(2) PCT)

The subject-matter of present claims 1-20 and 22 fulfills the requirements of Art. 33(2) PCT.

2.1 Document D3 (see D3, page 3, lines 3-10 and eg. example 3 on page 6)

discloses eg a composition containing a eutectic solution of 4 g ibuprofen and 4 g menthol, also mixed with benzyl alcohol, carbomer and water. However, none of the compositions of D3 contains an emulsifying agent. Therefore, the subject-matter of present independent claim 1 and present independent claim 22 is new over D3.

- 2.2 Document D4 discloses a formulation, which is a gelled oil-in-water emulsion with an oil phase being a eutectic mixture of local anaesthetics. In a particular embodiment (see D4, example 1, page 18), the composition comprises an aqueous continuous phase with a polymeric emulsifier and an oil phase consisting of a eutectic mixture of lipocaine and tetracaine stated as being liquid at room temperature. However, present independent claim 1 and present independent claim 22 disclaim compositions comprising local anaesthetics. Thus, present independent claims 1 and 22 are new over D4.
- 2.3 Document D5 discloses a topical anaesthetic formulation based on a 1:1 eutectic mixture, having an eutectic temperature of 18°C, of lidocaine and prilocaine, emulsified in water. Present independent claim 1 and present independent claim 22 disclaim compositions comprising local anaesthetics. For this reason, present independent claims 1 and 22 are new over D5.
- 2.4 Document D6 discloses a stabilized pesticidal emulsion of the oil-in-water type (see D6, page 4, lines 39-45) comprising (see D6, pages 20-21, example 3):
  - an oil phase consisting of two pesticides: 191 g/l (2,4-dichlorophenoxy)acetic acid isooctyl ester (2,4-D IOE)and 208 g/l (2,4-dichlorophenoxy)propionic acid isooctyl ester (2,4-DP IOE),
  - a water phase containing surfactants and thickeners.

    Even though said pesticides are ingredients which are pharmacologically active and are liquid at room temperature (see D6, page 19, lines 33- 37 and page 7, lines 8-12), present independent claim 1 and present independent claim 22 refer to topical compositions for mutual enhancement of transdermal permeation of pharmacologically active ingredients. It is clear that compositions containing pesticides, ie substances which are virtually toxic to humans, are not topical compositions suitable for transdermal permeation in the meaning of the present application.

### 3 Inventive step (Art. 33(3) PCT)

Document D4 is devoted to an apparatus, a product formulation and a method for improved dermal permeation of pharmaceuticals. The subject-matter of D4 belongs also to the medical field and document D4 can be therefore considered as the closest prior art for present application.

As stated above (point 2.2), the subject-matter of present claim 1 differs from the known composition in that it does not contain local anaesthetics.

The problem to be solved by the present invention may therefore be regarded as how to enhance mutually the topical absorption of at least two drugs, regardless their nature (see present application p. 1, I. 3-12 and p. 4, I. 8-18).

Document D4 teaches the skilled person that a composition comprising a eutectic mixture of local anaesthetics is chemically more stable: the active ingredients are less subject to hydrolytic degradation. Even though document D4 points out that the device can be used for delivering a multitude of drugs, the teaching of D4, regarding a eutectic mixture, is confined to anaesthetics and more particularly to the their stability (see D4, p. 10, l. 6 - p. 13, l. 7). There is no incentive in D4 to consider the applicability of a eutectic mixture for anything other than hydrolysis-sensitive local anaesthetics, and even less for increasing the mutual enhancement of the topical absorption of at least two drugs. In D4, the improvement of the dermal permeation is due to heat supplied by the device, regardless of the formulation, eutectic or non-eutectic. The present application does not require the use of heat to achieve a similar aim.

For these reasons, the subject-matter of independent claim 1 seems to include an inventive step in the meaning of Art. 33(3) PCT.

This reasoning applies mutatis mutandis to the subject-matter of present independent claim 22.

- 4 Claims 2-20 are dependent on independent claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.
- For the assessment of the present claims 21 and 23 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the

use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment (present claim 22).

#### VII

- 1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D3-D5 is not mentioned in the description, nor are these documents identified therein.
- The description is not in conformity with the claims as required by Rule 5.1(a)(iii) PCT.

#### **CLAIMS**

- 1. A topical composition for mutual enhancement of transdermal permeation of at least first and second pharmacologically active agents, the composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of first and second pharmacologically active agents and the continuous phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C; and at least one compatible emulsifying agent, with the proviso that the at least first and second pharmacologically active agents are each not local anaesthetics.
- A topical composition according to Claim 1, in which the first pharmacologically active agent has a melting point between 35 and 75°C, preferably 40-50°C, and the second pharmacologically active agent has a melting point between -40°C and 150°C, preferably between -5 and 90°C.
- A topical composition according to Claim 1 or
   2, in which the topical composition additionally includes, in the eutectic mixture, a third pharmaceutically acceptable component.

- 4. A topical composition according to Claim 3, in which the third pharmaceutically acceptable component has a melting point between 40 and 150°C, preferably between 40 and 75°C.
- 5. A topical composition according to Claim 3 or 4, in which the third component is a third pharmacologically active agent.
- 10 6. A topical composition according to any one of Claims 3-5, in which the topical composition additionally includes, in the eutectic mixture, a fourth pharmaceutically acceptable component.
- 7. A topical composition according to Claim 6, in which the fourth pharmaceutically acceptable component has a melting point between 40 and 150°C, preferably between 40 and 75°C.
- 20 8. A topical composition according to Claim 6 or 7, in which the fourth component comprises a fourth pharmacologically active agent.
- 9. A topical composition according to any one of
  the preceding claims, in which said at least one
  discontinuous phase contains no co-solvent or
  additional oil phase, so that the eutectic mixture
  substantially, preferably essentially, comprises the or
  each discontinuous phase of the emulsion.

- 10. A topical composition according to any one of the preceding claims, in which the first pharmacologically active agent is selected from triclosan, chlorocresol, chlorbutanol, methyl nicotinate, triprolidine, promethazine, trimeprazine, sulfiram, oxybutynin, capsaicin, testosterone enanthate or choline salicylate.
- 11. A topical composition according to any one of the 10 preceding claims, in which the second pharmacologically active agent is selected from triclosan; chlorocresol, capsaicin, trimeprazine, choline salicylate, methyl nicotinate; non-steroid anti-inflammatory agents selected from arylpropionic acid derivatives such as 15 ibuprofen, ketoprofen, fenoprofen and flurbiprofen; aryl acetic acid derivatives such as etodolac; and arylcarboxylic acids; narcotic analgesics such as fentanyl; anti-fungal agents such as econazole and ketoconazole; antibacterial agents such as mupirocin, 20 chlorbutanol, clindamycin and iodine; anticholinergics such as oxybutynin; anthelmintics such as tetramisole; antihistaminics such as triprolidine and promethazine and antihypertensives such as propranolol.

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12. A topical composition according to Claim 5 or 8, in which the third and fourth pharmacologically active agents are each selected from triclosan; chlorocresol; capsaicin, trimeprazine, choline salicylate, methyl

nicotinate; non-steroid anti-inflammatory agents selected from arylpropionic acid derivatives such as ibuprofen, ketoprofen, fenoprofen and flurbiprofen; aryl acetic acid derivatives such as etodolac; and arylcarboxylic acids; narcotic analgesics such as fentanyl; anti-fungal agents such as econazole and ketoconazole; antibacterial agents such as mupirocin, chlorbutanol, clindamycin and iodine; anticholinergics such as oxybutynin; antihypertensives such as propranolol; antihistaminics such as triprolidine and promethazine; and anthelmintics such as tetramisole.

- 13. A topical composition according to Claim 3 or 4, in which the third component is a pharmaceutically
  15 acceptable component selected from lauric acid, stearyl alcohol, menthol, thymol, cinnamic acid or an ester thereof.
- 14. A topical composition according to any one of the preceding claims, in which the pharmaceutically acceptable carrier is substantially hydrophilic, said carrier containing substantially, preferably essentially, water as the continuous phase.
- 25 15. A topical composition according to any one of the preceding claims, in which the pharmaceutically acceptable carrier contains at least one gelling or suspension agent.

16. A topical composition according to Claim 15, in which the gelling or suspension agent is selected from carbomers, modified cellulose derivatives, naturally-occurring, synthetic or semi-synthetic gums such as xanthan gum, acacia and tragacanth, modified starches, co-polymers such as those formed between maleic anhydride and methyl vinyl ether, colloidal silica and methacrylate derivatives or a mixture thereof.

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- 17. A topical composition according to any one of the preceding claims, in which the topical composition is in the form of a gel, lotion, suspension, cream, aerosol spray, transdermal patch, medicated dressing or soft gelatin capsule.
- 18. A topical composition according to any one of the preceding claims, in which the emulsifying agent is selected from non-ionic, cationic and anionic surfactants.
- 19. A topical composition according to Claim 18, in which the emulsifying agent is a non-ionic surfactant.
- 25 20. A topical composition according to any one of the preceding claims, in which the at least two pharmacologically active agents are structurally and/or pharmacologically diverse.

- 21. Use of a topical composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of at least first and second pharmacologically active agents and the continuous phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C; and at least one compatible emulsifying agent, with the proviso that the at least first and second pharmacologically active agents are each not local anaesthetics, for mutual enhancement of transdermal permeation of the at least first and second pharmacologically active agents.
- Use of an emulsion of at least one 15 discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of at least first and second pharmacologically active agents and the continuous phase being provided by a pharmaceutically acceptable carrier, the eutectic 20 mixture having a melting point below 40°C; and at least one compatible emulsifying agent, with the proviso that the at least first and second pharmacologically active agents are each not local anaesthetics, for the manufacture of a topical composition for mutual 25 enhancement of dermal permeation of the at least first and second pharmacologically active agents.

- A method for mutual enhancement of dermal 23. permeation of at least first and second pharmacologically active agents, the method comprising applying a topical composition for mutual enhancement of transdermal permeation of at least first and second pharmacologically active agents, the composition comprising an emulsion of at least one discontinuous phase in a continuous phase, the or each discontinuous phase including a eutectic mixture of first and second pharmacologically active agents and the continuous 10 phase being provided by a pharmaceutically acceptable carrier, the eutectic mixture having a melting point below 40°C; and at least one compatible emulsifying agent, with the proviso that the at least first and second pharmacologically active agents are each not 15 local anaesthetics, to an accessible body surface.
- 24. A topical composition according to any one of the preceding claims in which the eutectic mixture of at least two pharmacologically active agents is selected from the group consisting of ibuprofen methyl nicotinate, oxybutynin chlorbutol, triclosan oxybutynin, methyl cinnamate oxybutynin, chlorobutol testosterone enanthate, methyl nicotinate -
- 25 ketoprofen, triclosan econazole, sulfiram levamisole, promethazine triclosan, promethazine benzocaine and ketoprofen benzocaine.

# INTERICTIONAL SEARCH REPORT

Inic .dional Application No PCT/IE 98/00036

A. CL	ASSIFIC	MOITA	OF S	WBJECT	MATTER	
IPC	6	<b>A61K</b>	9/1	107	A61K45/	06

According to International Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  $IPC \ 6 \ A61K$ 

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT					
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X	WO 97 04728 A (ZHANG ET AL.) 13 February 1997 see page 18, line 14 - line 31	1,2,9, 14-18			
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Further documents are listed in the continuation of box C.	χ Patent family members are listed in annex.
Special categories of cited documents:  "A" document defining the general state of the art which is not considered to be of particular relevance  "E" earlier document but published on or after the international filling date  "U" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)  "O" document referring to an oral disclosure, use, exhibition or other means  "P" document published prior to the international filling date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  "&" document member of the same patent family
Date of the actual completion of the international search	Date of mailing of the international search report
28 September 1998	08/10/1998
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016	Benz, K

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